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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/815,825	ALLEN ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2005 and 19 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-11,17-22 and 49-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-11,17-22 and 49-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a reply to the Papers filed 31 May 2005 and 19 September 2005 in response to the Non-Final Office Action mailed 28 December 2004. Claims 1-5, 8-11, 17-23, 27-31, 33, 35, 42, 45 and 47 were considered in the 28 December Office Action. Claims 1-5, 23, 27-31, 33, 35, 42, 45 and 47 were canceled; claims 8, 10, 11 and 17-22 were amended; and claims 49-66 were added in the 19 September Paper. Claims 8-11, 17-22 and 49-66 are pending and under consideration.

This Office Action is made non-final in view of the new art cited herein below to support the rejection under 35 USC §112, first paragraph.

Response to Amendment

Rejection of claims 1-5, 23, 27-31, 33, 35, 42, 45 and 47 is rendered moot by the cancellation thereof.

Claim Rejections - 35 USC § 101

Rejection of claims 42, 45 and 47 under 35 U.S.C. 101 and 112, first paragraph, because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility is rendered moot by the cancellation of the claims. It is further noted that the rejection is not applied to the instant claims in spite of their expanded scope because it is acknowledged that there is an enabled embodiment within the scope of the claims. To the extent that they are relevant to the scope of enablement rejection (*Infra.*), Applicant's arguments regarding utility for the claimed invention are addressed herein below.

Claim Rejections - 35 USC § 112

Rejection of claims 17-22 under 35 USC §112, first paragraph, as lacking enablement for the full scope of the claimed subject matter is **withdrawn**. First, Applicant argues persuasively in the fourth paragraph on page 19 of the 31 May Paper that the specification defines a "cGMP phosphodiesterase gene" as limited to comprising the target gene as reduced to practice in the application. Furthermore, claims 17-22 limit the eye abnormality to the disclosed abnormalities which reasonably correlate with retinitis pigmentosa as described at page 60 of the specification. Therefore, the skilled artisan would be able to make and use the claimed mouse without undue experimentation.

Claims 8-11 **stand rejected** and newly added claims 49-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse comprising a homozygous disruption in a cGMP phosphodiesterase alpha subunit gene, wherein the mouse lacks production of a functional cGMP phosphodiesterase alpha subunit and exhibits an eye abnormality consistent with retinitis pigmentosa and methods of making and using the mouse, does not reasonably provide enablement for any transgenic mouse comprising a null endogenous cGMP phosphodiesterase alpha subunit gene. The rejection is maintained for reasons of record and herein below in the response to arguments.

As stated in the previous Office Action, "Although…the specification asserts that the claimed mouse is useful as a model of disease and provides a unique animal model for testing and developing new treatments relating to the phenotype and provides generic teachings regarding screening for compounds capable of ameliorating disease symptoms. The specification

fails to disclose how the phenotypic characteristics of the mouse, other than those consistent with retinitis pigmentosa, are correlated with a pathological state such that the skilled artisan would be able to use the mouse to develop treatments relating to those phenotypes" (third paragraph on page 9) and "because neither the art nor the instant disclosure teach the skilled artisan how embodiments falling within the broad scope of an eye abnormality, other than those consistent with retinitis pigmentosa, can be used as a model of disease, one of ordinary skill would have to experiment to establish which eye abnormalities can be reasonably correlated with a disease state such that the mouse can be used to identify a compound useful in the treatment of disease" (paragraph bridging pages 10-11).

Response to Arguments

In response to the *prima facie* case of record, Applicant has amended claims 8, 10 and 11 such that the claimed invention is no longer limited to exhibiting any phenotype at all and added new claims 49-66, which either do not limit the claimed mouse to exhibiting a phenotype or recite one of the various disparate phenotypes as set forth on pages 60-61 of the specification.

In the remarks, Applicant submits that the rejection does not distinguish between predicting *a priori* the phenotype of a knockout mouse and the reproducibility of a knockout mouse taught in the specification. Applicant contends, "the Examiner has not cited any support for the position that one skilled in the art would not be capable of reproducing the claimed mouse having the phenotypes described in the specification" (sixth paragraph on page 19). Applicant cites Doetschman as teaching "The conclusion will be that the knockout phenotypes do, in fact, provide accurate information concerning gene function" (emphasis added by Applicant).

Applicant points out, with regard to the effect of background, the mice were generated from ES cells derived from the 129/OlaHsd mouse substrain to generate chimeric mice. The F1 mice were generated by breeding with C57BL/6 females, the observed phenotypes were observed by comparing cGMP phosphodiesterase -/- mice with cGMP phosphodiesterase +/+ mice of identical background and requests that the Examiner explain how background could have caused the reported phenotypes when the transgenic mice and the control mice were of identical background. Applicant contends that the Dryja paper cited by the Examiner only supports the Applicant's position that the asserted utility is credible substantial and specific.

These arguments have been fully considered but are not deemed persuasive. Many of the presently rejected claims, in contrast to the previously rejected claims, do not limit the claimed mouse to exhibiting any phenotype at all. With regard to Applicant's contention that the Examiner has not cited any support for the position that one skilled in the art would not be capable of reproducing the claimed mouse having the phenotypes described in the specification, Applicant is directed to the statement in the paragraph bridging pages 8-9 of the previous Office Action, which reads, "Doetschman goes on to teach, 'it has become clear that genetic background plays an important role in the susceptibility of mice to many disorders. Therefore, the phenotypes of knockout mouse strains will also have genetic background dependencies'". The passage from Doetschman cited in the Office Action goes on to provide the example of the *Tgfb1* gene knockout which exhibits dramatically different phenotypic characteristics depending upon the genetic background of the mouse (paragraph bridging pages 140-141). With regard to the instant claims, although it is acknowledged that a knockout mouse whose genome comprises a homozygous disruption in a cGMP phosphodiesterase alpha subunit gene, wherein the mouse

lacks production of a functional cGMP phosphodiesterase alpha subunit and exhibits an eye abnormality consistent with retinitis pigmentosa is enabled by the specification, the rejected claims are not limited to exhibiting that phenotype. In view of the unpredictable relationship of genotype to phenotype evidenced by the teachings of Doetschman, the skilled artisan would not expect that all mice comprising a null endogenous cGMP phosphodiesterase alpha subunit allele would exhibit an eye abnormality consistent with retinitis pigmentosa. Therefore, the skilled artisan would have to determine experimentally the useful properties of those mice.

With regard to the wide variety of other phenotypes recited in the claims, including inflammation of the aorta, tubular dilation or pyelitis of the kidney, extramedullary hematopoiesis of the liver, lymphoid hyperplasia, lymphoid atrophy, hemorrhage of the lymph nodes, *etc.* It is unclear from the disclosure that these phenotypes are even characteristic of the knockout mouse reduced to practice in the application. The passage that describes the homozygous knockout mice reduced to practice states, "[t]he homozygous mice demonstrated at least one of the following phenotypes" (page 60; emphasis added). Although the description of the eye abnormalities is set forth as a positive statement (*i.e.*, "Homozygous mice demonstrated eye abnormalities..."), the remaining phenotypes are stated as alternatives (*e.g.*, "The kidney abnormalities included tubular dilation or pyelitis"; emphasis added), which, in the case of lymphoid hyperplasia and lymphoid atrophy (page 60, lines 24-25) are apparently mutually exclusive. Thus, it is unclear whether many of the various phenotypes recited in the claims are actually exhibited by the mice reduced to practice or whether those phenotypes are set forth as prophetic examples. Furthermore, as discussed in the previous Office Action, a number of human patients comprising homozygous disruptions of the rod cGMP phosphodiesterase alpha are

known in the art (Dryja *et al.*, cited at page 5 of the 28 December Office Action). However, the Examiner can find no evidence that any of the phenotypes recited in the claims are characteristic of disruptions of the PDE6A gene, which encodes the cGMP phosphodiesterase alpha subunit, in humans, or are exhibited by human retinitis pigmentosa patients. Therefore, it is not clear that mice comprising homozygous a null endogenous phosphodiesterase alpha subunit allele and exhibiting one of the recited phenotypes, other than a retinal abnormality consistent with retinitis pigmentosa, would be a valid model for any pathological state. Therefore, the skilled artisan would have to determine how the mouse could be used by empirical experimentation.

In the section entitled "*The Claimed Transgenic Mice Have a Well-established Utility*" commencing on page 8, Applicant argues that all knockout mice have a well-established utility regardless of the phenotype exhibited by the mouse. Applicant asserts, "[t]he present invention has a well-established utility since a person of ordinary skill in the art 'would immediately appreciate why' knockout mice are useful. As a general principal, a knockout mouse has the inherent and well-established utility of defining the function and role of the disrupted target gene, regardless of whether the inventor has described any specific phenotypes, characterizations or properties of the knockout mouse" (page 8). Applicant urges, "the knockout mouse has been accepted by the NIH as the premier model for determining gene function, a utility that is specific, substantial and credible" (page 9). In support of this contention, applicant cites various statements from the art expressing enthusiasm for the use of the knockout mouse to determine gene function. Applicant asserts that the well-known use of the claimed mouse is in characterizing the function of the cGMP phosphodiesterase α gene that has been deleted therefrom. Applicant cites excerpts from an NIH website, Austin *et al.*, Lewin, Joyner, Matise

and Albert's Molecular Biology of the Cell in establishing that knockout mice are invaluable tools of scientific research (pages 9-13). Applicant also cites the MPEP in discussing the utility of research tools (page 11 of the 7 March Paper and MPEP 2107.01,I).

However, the Office does not recognize the general utility of a knockout mouse for studying the function of a gene deleted therefrom as a patentable utility. A well-established utility and a utility with a particular practical purpose is one that is specific and substantial. With respect to the references cited by Applicant, the validity of the opinion of the NIH and Bruce Albert is not questioned. However the use of a mouse to determine the function of a gene deleted from the mouse as asserted by Applicant is not a specific and substantial patentable utility. Applicant cannot rely on general statements as to the value of transgenic animals as objects of basic research to establish a specific utility for the animal of the instant claims. Furthermore, with regard to "substantial utilities", MPEP 2107.01 states, "the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a 'real world' context of use and, therefore, do not define 'substantial utilities': (A) Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved...(C) A method of assaying for or identifying a material that itself has no specific and/or substantial utility..." In *Brenner, Comr. Pats. v. Manson,* 148 USPQ 689 (US SupCt 1966), the Supreme Court found that there is a distinction between scientific utility, which is evidenced in the articles cited by Applicant, and patentable utility under 35 USC §101. The Court states, "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing...This is not to say that we mean to disparage the importance of contributions to the fund of scientific information short of

the invention of something 'useful', or that we are blind to the prospect that what now seems without 'use' may tomorrow command the grateful attention of the public. But a patent is not a hunting license. It is not a reward for the search, but compensation for its successful completion" (page 696).

Applicant's assertion that the particular phenotype exhibited by the mouse is irrelevant to using claimed invention because the mouse can be used to define the function of the gene knocked-out from the mouse is not a substantial utility because it amounts to using the animal as an object of use-testing. Beyond contributing to the fund of scientific knowledge, the only purpose of determining the functional properties of the cGMP phosphodiesterase gene is to discover a 'real-world' utility for the mouse or the gene. This is not a patentable utility.

Furthermore, given the unpredictable nature of the art, the utility of any given transgenic animal must be established individually. Applicant is again reminded that the relationship of the phenotype displayed by a mouse comprising a mutation in any given gene is highly dependent on genetic background. This fact is well known to one of ordinary skill in the art. For example, Gerlai *et al.* (1996) *Trends Neruosci.* 19:177-181 teaches:

> The functional relevance of gene targeting has been questioned because the mutation might lead to an avalanche of compensatory processes (up- or downregulation of gene products) and resulting secondary phenotypical changes. Clearly, a null-mutant organism might not only lack the product of a single gene but might also possess a number of developmental, physiological, or even behavioral processes that have been altered to compensate for the effect of the null mutation. Therefore, one might expect an array of complex phenotypical changes that might not be directly related to the function of the gene of interest. Teasing out the primary and secondary changes will require co-ordinated efforts of scientists from several fields of biology. However, these efforts might be conduced in vain if the effects of genes other than those of the one targeted have not been ruled out with certainty.

Furthermore, Wolfer *et al.* (2002) *TRENDS Neurosci.* 25 :336-340 teaches that mice created as described by Applicant (*supra*) comprise not only the induced null mutation, but also 129 genes from the ES cells. Thus, a linkage disequilibrium will exist for genes linked to the target gene because animals comprising the target gene will also comprise the linked 129-derived alleles and mice that do not comprise the target gene will comprise alleles of the background strain (see especially the paragraph bridging the first and second columns on page 336). Thus, without experimental characterization of the animal, the skilled artisan does not know which phenotypic characteristics are a result of the target gene ablation and which are a result of linkage disequilibrium of genes linked to the target gene. Therefore, the skilled artisan must establish which phenotypes provide an accurate representation of target gene function by empirical experimentation.

Thus, while there is no question that transgenic animals, as a class of invention, can be used to study genes (although this by itself is not a patentable utility), the utility of any given transgenic animal must be established experimentally.

Applicant likens the claimed transgenic mouse to a research tool such as a gas chromatograph or screening assay. On page 11, Applicant cites MPEP §2107.1, I and emphasizes the statement, "[m]any research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility..." However, the remainder of that same paragraph reads, as quoted by applicant, "[a]n assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact 'useful' in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and

inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as 'research tool', 'intermediate' or 'for research purposes' are not helpful in determining if an applicant has identified a specific and substantial utility for the invention."

Viewed as a whole, this paragraph is clearly an admonition against concluding that an invention lacks utility simply because it can be labeled a research tool. Obviously the converse is also true, and an argument that an invention has patentable utility because it is a 'research tool' is as invalid as arguing that research tools have no patentable utility. Instead, utility must be assessed based on the particulars of the invention and the disclosure. A gas chromatograph, is a research tool with a well-defined function and highly specific use that does not necessitate further study of itself. A tool such as a gas chromatograph may be used for a variety of analyses of other products; however, this does not change its specific use for analyzing a sample. In contrast, the claimed invention is not a general tool for analyzing other samples and, at most, serves to study the function or characteristics of itself. An assertion that a knockout mouse can be used to study the functional properties of the missing gene is akin to asserting that a gas chromatograph is useful for determining the properties of a GC column, wherein the useful properties of the GC column are unknown. While gas chromatographs can be used for this purpose, it would not be considered a patentable utility because it only serves to identify the useful properties of the invention itself.

On page 12, Applicant asserts that commercial use and acceptance is an important indication that the utility of an invention has been recognized by one of skill in the art and alleges that subscriptions to a database comprising data obtained from the claimed invention and

orders for the claimed mouse from at least one large pharmaceutical company demonstrates the practical utility of the claimed invention.

Declaration of Robert Driscoll Pursuant to 37 C.F.R. §1.132

Applicant submits a Rule 132 declaration from Robert Driscoll, Vice President of lntellectual Property & Legal Affairs of Assignee, Deltagen as evidence of sales and purpose of such use. The declaration states that the claimed mouse has been purchased by at least one pharmaceutical company. Declarant asserts that the company is one of the ten largest pharmaceutical companies in the world (although the identity of the company is not disclosed) and that the company purchased the claimed mouse for studying gene function and for human therapeutic drug development. Applicant submits that it runs contrary to common sense to think that one of the world's largest pharmaceutical corporations would purchase the claimed mouse if it thought the mouse had no utility.

This argument and the showings of the declaration have been fully considered but are not deemed persuasive. For the reasons set forth in the previous Office Action and herein above, the skilled artisan would not be able to use the claimed invention beyond the scope of those embodiments which exhibit a retinal abnormality consistent with retinitis pigmentosa without having to determine the useful properties of the mouse. The purchase of data generated with the mouse or the purchase of the mouse itself does not obviate this conclusion. Furthermore, the showings of the declaration do not establish commercial success as asserted by Applicant. The showings of the declaration are not sufficient to support Applicant's assertion of commercial

success. MPEP §716.03(b) IV states, "Gross sales figures do not show commercial success absent evidence as to market share, *Cable Electric Products, Inc. v. Genmark, Inc.,* 770 F.2d 1015, 226 USPQ 881 (Fed. Cir. 1985), or as to the time period during which the product was sold, or as to what sales would normally be expected in the market, *Ex parte Standish,* 10 USPQ2d 1454 (Bd. Pat. App. & Inter. 1988). The declaration does not include any sales figures and does not provide any evidence to establish market share, the time period during which the product was sold or evidence as to what sales would normally be expected in the market. Therefore, the declaration does not establish commercial success.

Finally, commencing in the first full paragraph on page 18, Applicant asserts that the claimed transgenic mice are useful for studying gene expression because mice within the scope of the claim contain a visible marker such as a lacZ gene. Applicant urges that the claimed transgenic mouse, regardless of any disclosed phenotypes, has inherent and well-established utility in the study of the function of the gene and determine where the gene is expressed. However, it is noted that the instant application does not appear to disclose an embodiment of the claimed invention configured so as to enable the study of gene expression. Such a construct would require that the visible marker gene comprised by the introduced construct be configured such that expression of the marker gene is driven by the endogenous promoter. The instant claims are not limited to comprising a visible marker gene configured such that the marker gene could be used to determine where the gene is expressed. The only mention of a LacZ reporter is found on page 61 of the specification, which states, "***LacZ Expression Analysis*:** LacZ (beta-galactosidase) expression was detected in the thyroid glands, salivary glands proper, salivary glands of the larynx, peritrachial and submucosal glands of the trachea and the mucous glands of

the tongue." However, there is no description of the LacZ construct comprised by the mouse (*e.g.*, did it comprise a promoter?). In that regard, it is noteworthy that the specification does not report any expression of the LacZ gene in retinal tissues even though, based on the discussion in the third paragraph on page 60, may other aspects of the eyes of the mice reduced to practice were carefully analyzed. Thus, it is unclear from the disclosure precisely what the LacZ data set forth on page 61 of the specification represent. Therefore, even if one were to accept, *arguendo*, that a transgenic mouse limited to comprising a visible marker gene configured such that expression of the marker gene represents expression of the endogenous gene, the claims are not so limited and there does not appear to be support for that embodiment in the disclosure as originally filed.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Using the claimed invention beyond the scope indicated as being enabled herein above would clearly require undue experimentation. Therefore, the claims are properly rejected as failing to meet the enablement requirement of 35 USC §112, first paragraph.

New Grounds

Claim Objections

Claims 10 and 17 are objected to because of the following informalities:

Claim 10 is objected to because the phrase, "the comprising the cGMP" in line 1 of part (a) is grammatically incorrect. Likewise, the phrase "said the eye" in line 1 of claim 17 is grammatically incorrect. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-11, 17-22 and 49-66 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The MPEP states, "[i]f new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. §112, first paragraph-written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." (MPEP § 2163.06). The MPEP further states, "[w]henever the issue arises, the fundamental factual inquire is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in the application" (*Id.*, § 2163.02). The introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first

paragraph. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996).

In the instant case, the claim 8 has been amended to recite that the transgenic mouse comprises a "null endogenous cGMP phosphodiesterase alpha subunit allele". In support of the limitation, applicant cites page7, lines 30-33 of the specification which states, "a 'transgenic animal' is an animal that contains within its genome a specific gene that has been disrupted by the method of gene targeting. The transgenic animal includes both the heterozygote animal (*i.e.*, one defective allele and one wild-type allele) and the homozygous animal (*i.e.*, two defective alleles)." Thus, the specification contemplates transgenic mice comprising defective alleles. However, the specification does not state that the defect comprised by the mouse is a null allele and there is no evidence provided in the disclosure that the mouse reduced to practice comprises a null allele (*i.e.*, does not express any protein). Therefore, the amendment of the claims to recite that the mouse comprises a null allele constitutes impermissible new matter.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 55 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim recites that, relative to a wild-type control mouse, the claimed mouse exhibits adventitia. As adventitia, *i.e.*, the outermost layer of a vessel or organ, is present in all mice, it is unclear how a transgenic mouse could exhibit adventitia relative to a wild-type mouse.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 8-10 and 49-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Qin *et al.* (1992) *J. Biol. Chem.* 267:8458-8463 (previously made of record) in view of Tsang *et al.* (1996) *Science* 272:1026-1029 (previously made of record) and Dryja *et al.* (*supra*).

Claim 8 is directed to a transgenic mouse comprising a null endogenous cGMP phosphodiesterase alpha subunit allele and has been amended such that the claim does not limit the transgenic mouse to exhibiting a phenotype.

As described in the previous Office Action, Qin *et al.* teaches a nucleic acid molecule comprising a nucleic acid sequence homologous to a cGMP phosphodiesterase alpha subunit gene. Qin *et al.* does not teach that the sequence should be configured as a targeting vector comprising a selectable marker gene located between the first and second polynucleotide sequences or producing a transgenic mouse using the nucleic acid.

Tsang *et al.* teaches construction of a targeting vector having the structural characteristics of the targeting vector disclosed in the instant application, except for the inclusion of a cGMP phosphodiesterase alpha subunit gene (see especially Figure 1A and the caption thereto), for the purpose of generating a transgenic mouse comprising a homologous disruption of the cGMP phosphodiesterase gamma subunit gene and production of a transgenic mouse whose genome comprises a null endogenous cGMP phosphodiesterase gamma subunit (see especially Figure 1D). Tsang *et al.* teaches that mice constructed in this way are useful to study the role of the cGMP phosphodiesterase subunit in retinal degeneration (paragraph bridging the middle and right columns on page 1026).

Dryja *et al.* teaches that mutations in the rod cGMP phosphodiesterase alpha subunit gene are linked to retinitis pigmentosa in humans (See *supra*).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to construct a targeting vector according to the teachings of Tsang *et al.* using the nucleic acid encoding a cGMP phosphodiesterase alpha subunit gene according to the teachings of Qin *et al.* to produce the transgenic mouse comprising a null endogenous cGMP phosphodiesterase alpha subunit allele.

One would be motivated to combine these teachings in view of the teachings of Dryja *et al.* and Tsang *et al.* Dryja *et al.* teaches that cGMP phosphodiesterase alpha gene disruptions correlate with retinitis pigmentosa in humans, and Tsang *et al.* teaches that disruption of cGMP phosphodiesterase subunits in mice results in retinal degeneration analogous to retinitis pigmentosa. In view of these teachings, the skilled artisan would be motivated to make the targeting constructs in order to investigate the role of the cGMP phosphodiesterase α subunit gene in retinitis pigmentosa. Absent evidence to the contrary, one would have a reasonable expectation of success in combining these teachings because construction of transgenic mice is routine in the art.

Although, for the reasons set forth in previous Office Actions and herein above, the phenotypic characteristics resulting from any given genotypic modification are unpredictable, the mouse of the instant claims is not limited to exhibiting any particular phenotype. Therefore, one would have a reasonable expectation of success in making the mouse of the instant claims.

Furthermore, with respect to the dependent claims, Tsang *et al.* teaches isolation of retinas from transgenic animals for use in experimental analyses, which retinal isolates would comprise cells obtained from the mouse (see especially Figures 3 and 4 and the captions thereto). Therefore, the cell obtained form the mouse according to claim 9 would also have been obvious to the skilled artisan in view of the teachings of Qin *et al.*, Tsang *et al.* and Dryja *et al.* Likewise, in the first full paragraph in the right column on page 1026, Tsang *et al.* teaches a method of producing a transgenic mouse comprising each of the process steps of the method of claim 10; teaches heterozygous intermediates in the production of the homozygous knockout mouse according to claim 49 (see especially Figure 1(C)); and teaches mice homozygous for the null

allele according to claim 50 (see especially Figure 1(D)). Finally, Tsang *et al.* teaches the targeting construct comprising the neomycin resistance selectable marker gene according to claims 51 and 52 Figure 1A.

In view of the foregoing, the invention of each of the instant claims 8-10 and 49-52, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a) as obvious over the art.

Claims 8 and 51-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Qin *et al.* in view of Tsang *et al.* and Dryja *et al.*, as applied to claims 8, 51 and 52 herein above, and further in view of Le Mouellic *et al.* (1990) *Proc. Natl. Acad. Sci. USA* 87:4712-4716.

For the reasons set forth herein above, the transgenic mouse of claims 8, 51 and 52, as a whole, would have been obvious to one of ordinary skill in the art at the time the instant invention was made. Qin *et al.* in view of Tsang *et al.* and Dryja *et al.* does not teach that the null cGMP phosphodiesterase allele should comprise a lacZ gene.

Le Mouellic *et al.* teaches a targeting vector comprising a lacZ visible marker gene constructed such that insertion of the marker gene into the genome of a mouse by homologous recombination provides the lacZ marker gene under the regulatory control of the ablated gene (see especially Figure 1, the caption thereto and the discussion in the first through third full paragraphs in the right column on page 4715).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Qin *et al.* in view of Tsang *et al.* and Dryja *et al.* according

to the teachings of Le Mouellic *et al.* to include a lacZ gene visible marker in the targeting vector used to produce the cGMP alpha subunit knockout mutant mouse.

Motivation to combine these teachings comes from Le Mouellic *et al.*, who states in the second full paragraph on page 4712 (citations omitted):

> Understanding the effects of gene inactivation would be easier if we could follow at the cellular level the eventual appearance of the phenotype induced by a defined mutation, dominant or recessive. Methods used to date to inactivate genes by homologous recombination [] do not easily allow one to follow the fate of cells that normally would express that gene. We have developed a procedure whereby a chosen gene is not only inactivated but also replaced by the functional reporter gene of *Escherichia coli* for β-galactosidase (*lacZ*). The endogenous promoter of the targeted gene controls the reporter gene, whose expression can be followed *in situ* throughout embryogenesis of the mutant animal.

These teachings demonstrate that the inclusion of a lacZ reporter gene in targeting constructs was known in the art at the time of filing and that the inclusion of a lacZ reporter was considered desirable because it allows one to follow expression of the targeted gene in the mouse comprising the targeting construct.

Absent evidence to the contrary, one would have a reasonable expectation of success in combining these teachings because Le Mouellic *et al.* provides detailed instruction of the process of constructing a targeting vector capable of providing a lacZ gene under the regulatory control of the targeted gene. With regard to using the mouse comprising the lacZ gene, Applicant is reminded that the art need only teach how to make what is claimed and need not demonstrate that the product possesses a patentable utility.

For these reasons, the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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